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EPILEPSY IN CYTOGENETIC ABNORMALITIES: PREVALENCE, PHENOTYPE CLASSIFICATION, AND PROGNOSTIC FACTORS

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Abstract:

Background*: Many chromosomal abnormalities are associated with Central Nervous System (CNS) malformations and other neurological alterations, among which seizures and epilepsy. Certain chromosomal syndromes are specifically associated with epilepsy and show a particular clinical and EEG pattern. This retrospective research proposal will study the prevalence of epilepsy in cytogenetic abnormalities, its classification and the prognostic factors regarding the response to Anti-epileptic medications (AED).*

Objective*: The present study aims at exploring prevalence of epilepsy in cytogenetic abnormalities, its classification and Prognostic factors of responsiveness to anti-epileptic medication.*

Design and Setting: *a retrospective study that was carried out in Prince Sultan Military Medical City, Riyadh, Saudi Arabia, that included a review of all chromosomal abnormalities (2010-2018). The chromosomal abnormalities were detected by chromosomal study, FISH, or array CGH . All patients with chromosomal abnormalities who develop epilepsy were included. Detailed clinical assessment was done through recording seizures, EEG, and MRI brain finding.*

Statistical analysis: *Data were represented in terms of frequencies and valid percentages for categorical variables. The analysis was done using SPSS version 26.*

Results: *550 patients were included in this study. The prevalence of seizures in the whole cohort was 14.7%, with 45.7% of females and 54.3% of males having seizures. Additionally, 44.4% of the whole cohort had a chromosomal micro-deletion abnormality, followed by 23.5% with chromosomal micro-duplication. As for the age of onset, 48% of patients with seizures had their first seizure at the age of less than one-year-old. 52.5% of the patients had generalized seizures followed by focal epilepsy in 29.4% of patients. 41.1% of patients with seizures showed unremarkable findings on Brain MRI, and congenital brain malformations in different chromosomal aberrations 27.6 % and 11.1% had a Lennox-Gastaut syndrome (LGS) after treatment*

Conclusion*: Epilepsy in patients with cytogenetic abnormalities appears to have a higher incidence in Saudi Arabia compared to western countries. Genetic deletions and duplications are the most common predictive factors for the occurrence of epilepsy.*

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1.INTRODUCTION:

There is a various range of chromosomal abnormalities that are linked to Central Nervous System disorders that may result in mental retardation or seizures that may increase the morbidity of patients, especially at a young age [1]. Some specific chromosomal syndromes are mainly linked to epilepsy, showing specific EEG and clinical features [2].

These genetic abnormalities include ring 20 chromosome syndrome, 1p36 monosomy, 18q-syndrome, Down syndrome, Miller-Dieker syndrome, Wolf-Hirschhorn syndrome [3]. On the other hand, other chromosomal disorders arising from other chromosomal disturbances were not correlated to increased risk of seizures such as Fragile-X syndrome, and Klinefelter syndrome [4].

Recent studies have shown that more than two hundred chromosomal disorders can lead to epilepsy or can have epilepsy as part of their chromosomal disease [5]. Some of these disorders can be linked to a mutation in a DNA sequencing or other micro-chromosomal alterations [6].

Despite the availability of data on the correlation between epilepsy and chromosomal abnormalities, data in the gulf area on epilepsy and chromosomal disorders is scarce and require further investigations, especially in Saudi Arabia.

Therefore, the present investigation aims to explore the prevalence, classification of epilepsy, as well as chromosomes that are correlated to epilepsy in Riyadh, Saudi Arabia.

2. MATERIALS AND METHODS:

Study design:

This is a retrospective cohort study that included pediatric patients in Prince Sultan Military Medical City, Riyadh, Saudi Arabia, in the duration between the year 2010 and 2018. All patients with chromosomal abnormalities who develop epilepsy were included.

Data collection:

Data from patients' charts were collected in a pre-designed excel sheet. The data included age of seizures onset, semiology of seizure, MRI findings, type of chromosomal abnormality, the outcome of treatment, and the use of medications to control epilepsy.

Statistical analysis:

All data were recorded in a pre-designed and validated excel sheet. Data were represented in terms of frequencies and valid percentages for categorical variables. Data were analyzed using IBM SPSS (Statistical Package for the Social Science; IBM Corp, Armonk, NY, USA) to perform all statistical calculations, version 26 for Microsoft Windows.

Ethical considerations:

Institutional research ethics board approval was acquired from Research Ethics committee of Prince Sultan Military Medical City, which hold code 1158 at January 2019.

3. RESULTS:

3.1 Patients demographics

This study included five hundred and fifty patients who had different chromosomal abnormalities and admitted to Prince Sultan Military Medical City, Riyadh, Saudi Arabia. The prevalence of seizures in the whole cohort was 14.7%, with 45.7% of females and 54.3% of males having seizures. Distribution among males and females is shown in (table 1).

Table 1. Prevalence of seizures among both genders

	Females		Males	
	N	%	N	%
Seizures	34	45.7	44	54.3
No Seizures	230	49.0	239	51.0

Data on the age of seizures onset was also collected. Age of onset ranged between less than one year and up to 14 years old. It has been demonstrated that 48% of patients with seizures had their first seizure at the age of less than one year old, as shown in (table 2).

Table 2. Age of onset of seizures

Age of onset	Frequency	Percent
Less than 1 Year	39	48
1 Year	3	3.7
13 months	1	1.2
15 months	1	1.2
20 months	2	2.5
Two years	3	3.7
30 months	2	2.5
Three years	5	6.2
Four years	4	4.9
Five years	2	2.5
Six years	1	1.2
Seven years	2	2.5
Eight year	1	1.2
Nine years	2	2.5
>10 Years	6	7.4

The type of chromosomal abnormality was examined. Different Types with Different prevalence of seizure was reviewed. 44.4% of the whole cohort had a chromosomal deletion abnormality, followed by 23.5% with chromosomal duplication. For example, Down Syndrome (Trisomy 21) has 13% with seizure of different Types. All patients with Angelman Syndrome (15q11 micro-deletion) developed epilepsy 100% (Table 3).

Table 3. Types of chromosomal abnormalities with seizure.

Cytogenetic Abnormalities	**Frequency**	**Percent**
Down syndrome (21 Trisomy)	10	13
DiGeorge Syndrome (22q11 micro-deletion)	4	5.1
Angelman Syndrome (15q11 micro-deletion)	5	6.4
William Syndrome (7q11.23 deletion)	4	5.1
1q micro-deletion	6	7.1
2q micro-deletion	3	3.1
3q micro-deletion	5	6.1
7p micro-duplication	5	6.4
Patau syndrome (13 Trisomy)	2	2.5
16p micro-deletion	5	6.4
Turner Syndrome (45X)	1	1.2
Xp microduplication	3	3.8
Others	25	32.3

As for the type of seizure, 52.5% of the patients had generalized seizures followed by focal epilepsy in 29.4% of patients. On the contrary, the incidence of other types of seizures did not exceed 4%, as shown in (table 4).

Table 4. Types of seizures

Types of seizure	Frequency	Percent
Generalized seizure	41	52.5
Focal seizure	23	29.4
Infantile spasm	10	12.8
Early infantile epileptic encephalopathy	1	1.2
Others	3	3.8

Brain Magnetic Resonance imaging done for 68 patients. 41.1% of patients with seizures showed unremarkable findings on Brain MRI. While 16.1% of patients showed brain atrophy. Ischemic changes in 13.2% and congenital brain malformations in different chromosomal aberrations 27.6% (Table 5).

Table 5. Most common MRI findings in patients with Epilepsy.

Finding	frequency	percent
unremarkable	28	41.1
Brain atrophy	11	16.1
Thin corpus callosum	5	7.3
Thick corpus callosum	2	2.9
Agenesis corpus callosum	4	5.8
Focal infarction	9	13.2
pontocerbellar hypoplasia	2	2.9
Malformed hippocampi	4	5.8
Lissencephaly	2	2.9

The outcomes of some patients were also reported showing that 11.5% had a Lennox-Gastaut syndrome (LGS) after treatment, while 15.3% of patients had an epileptic encephalopathy, as shown in (table 6). Patients with good response and successfully discontinued Anti-Epileptic medications in 41%. Owing to the retrospective nature of the study, the outcome of the rest of the seizures patients could not be obtained.

Table 6. Outcome

	Frequency	Percent
Good response	32	41
Lennox-Gastaut Syndrome	9	11.5
Epileptic encephalopathy	12	15.3
intractable seizure	14	17.9
Unknown	11	14

One objective of this study, to know most epileptogenic chromosomal aberrations. All patients with Angelman syndrome had epilepsy in 100%. 3q micro-deletion is also developed epilepsy in 100%. 2q micro-deletion abnormalities 60%. Epilepsy occurs in 3% of individuals with Down syndrome, while Edward Syndrome (Trisomy 18) no seizure has been recorded. Epilepsy is an uncommon manifestation associated with 22q11 deletion (DiGeorge Syndrome). It is present in less than 16% of the patients as shown in (table 7).

Table 7. The Most Epileptic Chromosomal Abnormalities.

Chromosomal Abnormalities			
	Total number	With seizure	Percent
Angelmann Syndrome	5	5	100
Wlilliam Syndrome	10	4	40
Down Syndrome	476	10	3
DiGeorge Syndrome	25	4	16
1q micro-deletion	10	6	60
3q micro-deletion	5	5	100
7p micro-duplication	9	5	55
Turner Syndrome	27	1	3.7
Edward Syndrome	18	0	
Patau Syndrome	8	2	25
Xp microduplication	7	3	42
2q micro-deletion	5	3	60
16p micro-deletion	9	5	55
Wolf-Hirschhorn Syndrome (4p16.3 deletion)	2	1	50
Cri du chat syndrome	2	1	50
Klinefelter syndrome (47XXY)	13	1	7

4. DISCUSSION:

Epilepsy is a common neurological disease that has different etiologies [11]. Recent reports have shown that epilepsy could be related to different genetic abnormalities that could be identified in the early years of life [12]. However, the prevalence and clinical features of epilepsy in relation to chromosomal disorders in Saudi Arabia remain unclear [13].

The present work aimed at exploring the prevalence, classification of epilepsy, as well as chromosomes that are correlated to epilepsy in Riyadh, Saudi Arabia. The study revealed that the prevalence of seizures in the whole cohort was 14.7%, with 45.7% of females and 54.3% of males having seizures.

Additionally, 44.4% of the whole cohort had a chromosomal micro-deletion abnormality, followed by 23.5% with chromosomal micro-duplication. As for the age of onset, 48% of patients with seizures had their first seizure at the age of less than one-year-old. 52.5% of the patients had generalized seizures followed by focal epilepsy in 29.4% of patients. On the contrary, and 4% showed other seizure types. 41.1% of patients with seizures showed unremarkable findings on Brain MRI. While 16.1% of patients have brain atrophy, ischemic changes in 13.2% and congenital brain malformations in different chromosomal aberrations 27.6%. The outcomes of some patients were also reported showing that 11.5% had a Lennox-Gastaut syndrome (LGS) after treatment, while 15.3% of patients had an epileptic encephalopathy.

In the present study, the most epileptogenic type of chromosomal abnormalities are Angelman syndrome and 3q micro-deletion syndrome 100%. Epilepsy occurs in 3% of individuals with Down syndrome, while Edward Syndrome (Trisomy 18) no seizure has been recorded. Epilepsy is an uncommon manifestation associated with 22q11 deletion (DiGeorge Syndrome), less than 16%.

Another study that was carried out by Mefford et al. [15] that included 517 patients with chromosomal abnormalities and idiopathic epilepsy. Mefford et al. [15] revealed that the prevalence of epilepsy in patients with cytogenetic disorders was 8.9%. Additionally, Mefford et al. [15] revealed that in these patients, epilepsy was accompanied by other disorders, commonly autism, and schizophrenia.

Although the present study identified other comorbid conditions with epilepsy in patients with chromosomal disorders like mental retardation, global developmental delay, psychosocial impairment which could be as part of chromosomal abnormalities. The prevalence of the epilepsy was 14.7%, which was higher than that reported by Mefford et al. [15]. Furthermore, the present study examined the different types of epilepsy, revealing that generalized seizures are the most common type of seizures in patients with chromosomal abnormalities.

To our knowledge, this is the first study to explore the figure of epilepsy in patients with chromosomal disorders in Riyadh, Saudi Arabia. However, the present study had some limitations that may question the outcomes.

First, the study was performed in one center in Riyadh city, which may affect the external validity of the findings. Additionally, due to the retrospective nature of the study, some of the patients' data were not available, which might affect the reliability of outcomes.

Certain chromosomal syndromes are specifically associated with epilepsy and show a particular clinical and EEG pattern, some Exaples:

- Angelman Syndrome
  Angelman syndrome result from deletions within bands 15q11-q13 of the maternally derived chromosome. The clinical phenotype is characterized by microcephaly, frontal upsweep, prominent mandible, pointed chin, protruding tongue, and diffuse depigmentation. Moreover, patients show severe mental retardation, inappropriate laughter, ataxic gait, jerky movements, spasticity, and lack of speech. Epilepsy is very frequent affecting 100%. Seizure start before age of 3 years. Generalized seizure like GTC, myoclonic are the most common. The have specific EEG finding 1-3 Hz /s high amplitude anterior slow wave.
- Down syndrome:
  Epilepsy occurs in 3% of individuals with Down syndrome. Age of seizure onset is early within first 12 months. However epilepsy in Down syndrome is less common than in most mental retardation syndromes. All seizure types may occur, infantile spasm being most common (30%) with poor prognosis and difficult to treat and evolve to LGS. Brain malformation as brain atrophy and hypoxic ischemic insult play role in occurrence of epilepsy and refractory to AED.
- 1q micro-deletion syndrome.
  In this syndrome, characterized by microcephaly, severe mental retardation, clubfoot, abnormal posturing. Epilepsy developed in 60%; usually begin in the first 3 years of life, mainly generalized epilepsy. Good response to medication. MRI brain showed agenesis of corpus callosum.
- William Syndrome:

Williams's syndrome is a disorder caused by a 7q11.23 deletion. The clinical phenotype characterized by short stature, a varying degree of mental deficiency, and distinctive facial features. Such characteristic facial features may include a round face, full cheeks, thick lips, a large mouth, broad nasal bridge. 40% developed Epilepsy; all patients had generalized Type with good control by anti-epileptic medications. Brain MRI was unremarkable in all patients.

- DiGeorge Syndrome:
  It is called 22q11.2 deletion syndrome. Patients commonly have heart abnormalities that are often present from birth, recurrent infections caused by problems with the immune system, and distinctive facial features and low levels of calcium in the blood. Epilepsy is uncommon, presented in four patients (16%) out of total 25. Two patients with focal epilepsy and two with generalized epilepsy. Brain MRI unremarkable. Good response with anti-epileptic medications.
- Edward Syndrome:
  It is Trisomy 18. Affected individuals may have heart defects and distinctive facial features include a small, abnormally shaped head; a small jaw and mouth, clenched fists with overlapping fingers. Due to the presence of several life-threatening medical problems, many individuals with trisomy 18 die before birth or within their first month. In this cohort study, no seizure documented.
- Patau Syndrome:
  It Trisomy 13. Individuals with trisomy 13 often have heart defects, brain or spinal cord abnormalities, micro-ophthalmia, extra fingers or toes, cleft lip, cleft palate. Due to severe multiple congenital anomalies the mortality is > 80% within the first month of life. Seizures reported rarely (25%) even if a variety of developmental abnormalities of the brain is present as holoprosencephaly, callosal agenesis. In most cases, seizures develop during the neonatal period. Most are multifocal seizure.

- Wolf-Hirschhorn Syndrome:
  The minimal deleted segment causing the phenotype of Wolf-Hirschhorn syndrome is 4p16.3. Clinical findings are very distinct like microcephaly, high forehead, prominent nasal bridge, beaked nose and hypertelerosim. Severe mental retardation and high prevalence of seizures (60-70%) that include focal and generalized epilepsy, frequently drug resistant. Age of onset range from neonatal period to 9 months old. Brain Magnetic Resonance Imaging (MRI) the most frequent anomaly is corpus callosum hypoplasia.
- 7p micro-duplication syndrome:
  Focal epilepsy mainly temporal lobe epilepsy found in 55% with bimodal peak of incidence at first few months of life and 10 years of age. Seizure difficult to treat and brain MRI showed mesial temporal sclerosis.
- Turner Syndrome:
  Epilepsy is uncommon 3.7%. Most common seizure type is focal epilepsy, which easy to control and normal brain MRI.
- 3q micro-deletion:
  In this cohort, five patients have 3q micro-deletion, all of them developed epilepsy (100%). Two patients with infantile spasm, two with generalized epilepsy and one with focal epilepsy. High rate of drug resistant. No reported epilepsy in other literatures.
- Klinefelter syndrome (47XXY):
  The incidence of epilepsy in Klinefelter syndrome is around 7%. One case in this cohort developed febrile convulsion. Neuro-imaging studies failed to identify structural basis of seizures.

  - No case reports described epilepsy with chromosome 10 and 11 abnormalities.

5. CONCLUSION:

Epilepsy in patients with cytogenetic abnormalities appears to have a higher incidence in Saudi Arabia compared to western countries. Micro-deletions and micro-duplications are the most common predictive factors for the occurrence of epilepsy. These findings should help decision-makers in Saudi Arabia to develop screening programs for these genetic abnormalities in order to detect these genetic abnormalities as early as possible.

Further prospective and multicenter studies are urgently needed to improve our understanding of the clinical features of epilepsy in patients with cytogenetic disorders in Saudi Arabia on a national level.

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